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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,614	10/18/2005	Mitsuharu Hirai	TOYA114.009APC	4647

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EXAMINER	
BAUGHMAN, MOLLY E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/553,614	HIRAI, MITSUHARU	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/2006; 10/18/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9 are confusing because it cannot be determined what is encompassed by "a nucleotide sequence ending at the nucleotide number 247 in the nucleotide sequence of SEQ ID NO:1 and a length of 13 to 30 nucleotides," stated in claims 1 and 7. It is unclear how many and which sequences of SEQ ID NO:1 is comprised within the probe. For example, it is unclear if the length of 13 to 30 nucleotides all must consist of sequences in SEQ ID NO:1, or at least two sequences 5' or 3' of nucleotide number 247 of SEQ ID NO:1. Furthermore, it is also unclear what is specifically encompassed by "ending at nucleotide number 247." It is unclear whether the sequence comprises the nucleotide at nucleotide number 247 and sequences 3' to the nucleotide, or the nucleotide at nucleotide number 247 and sequences 5' to the nucleotide. While claims 2-6, and 8-9 do not particularly use the phrase, they depend from claims which use the phrase.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO 02/072875 A1) in view of Crockett et al. (2001).

Regarding claims 1-3, Lee et al. describe the use of a combination of mutated gene sequences from wild-type genes that are involved in insulin secretory function, one of which is S20G amylin (page 4, Summary of the Invention, 1st paragraph). Sequence ID NO:12, shown in Figure 5, is the nucleic acid sequence of the human amylin gene exon 3 with the S20G mutation (Brief Description of the Drawings, page 6), which comprises a nucleotide sequence complementary to a nucleotide sequence ending at the nucleotide number 247 in the nucleotide sequence of SEQ ID NO:1 of the instant invention [claim 1], as well as corresponding nucleotide sequences of SEQ ID NO: 12 and 13 [claim 2]. Lee et al. describe that "the nucleic acid probes of the invention are nucleic acid sequences from the mutated genes of interest. They are at least 8, 12, 15 or 20 base pairs in length, but can be 50, 80 or 100 base pairs in length, and include at least one associative mutation but may include multiple mutations and can be as long as the length of the transcribed gene" (page 14, last paragraph) [claim 1]. In one embodiment, a method comprises contacting a sample with a representative combination of at least two mutated genes of interest, subjecting the DNA to

hybridization to detect nucleotide differences of at least one base pair (page 4, Summary of the Invention, 2nd paragraph). This is done by attaching the mutated genes of interest to a microchip or other solid support (page 5, 2nd paragraph).

Lee et al. do not describe a probe comprising the 5' end labeled with a fluorescent dye, and in which fluorescence of the fluorescent dye decreases upon hybridization [claim 1]. They also do not describe a method for detecting a mutation comprising performing a melting curve analysis for a nucleic acid having a single nucleotide polymorphism site by using a nucleic acid probe labeled with a fluorescent dye and measuring fluorescence of the fluorescent dye, and detecting the mutation on the basis of a result of the melting curve analysis [claim 3].

Crockett et al. describe a method of using a single 5'-fluorescein probe in real-time PCR for quantification and genotyping. In their method, amplification was accompanied by a decrease in fluorescence corresponding to PCR product accumulation (page 90, results, and Figure 1B). They note that instead of an increase of fluorescence with increasing product concentration, quenching results in a decrease in fluorescence (page 93, 2nd column, 1st paragraph). In their studies, they analyzed varying the content and placement of specific nucleotide resides, particularly Gs, within the probes in correlation to the placement of the fluorescein and its opposing nucleotides residues in the target sequence (page 91). Using the information obtained from their modeling systems, they were able to design probes which optimized quenching during hybridization to analyze several polymorphisms within genes (pages 92-95). Their analysis concluded that "the extent that a fluorescein-labeled probe is

quenched by deoxyguanosine nucleotides on the complementary unlabeled strand depends on the position and dose of opposing G residues" and furthermore, "the first dangling base on the unlabeled strand should be a G" (page 95, 1st column, 2nd paragraph).

In genotyping assays of Crockett et al. using specifically designed fluorescein-quenching probes, homozygotes complementary to the probe melt at a relatively high temperature, homozygotes that are mismatched to the probe melt at a relatively low temperature (page 92, 1st column, first paragraph). In one assay, when genotyping hemoglobin mutations, they designed a probe homologous to the hemoglobin S sequence, which covered the polymorphic site and the fluorescein was placed opposite to two G residues (page 92, 2nd column, 1st paragraph, and Figure 6 description). The probe was included in the PCR amplification mixture with primers targeting the polymorphic region and Klen-Taq polymerase, and melting curve analysis was automatically performed after PCR (Figure 6 description). By using slow heating during the reaction, "a 'dynamic dot blot' is produced that identifies alleles by their melting temperature (page 94, 2nd column, first paragraph). "Derivative melting curves easily distinguish different genotypes by quenching from one (Figs. 7 and 8) or two (Figs. 5 and 6) Gs" (page 94, 2nd column, first paragraph).

Regarding claims 4-6, Lee et al. also discuss PCR analysis using primers designed to anneal to the wild-type gene sequence in regions that flank the mutation in a gene of interest (page 15, last paragraph). In Example 3, page 41, DNA fragments

spanning the mutation site of S20G of the amylin gene were amplified by PCR using primers of SEQ ID NO:30 and 31.

Regarding claims 7-9, Lee et al. also discuss a kit comprising a solid support having attached to it a representative array of nucleic acid sequences, each with a mutation or polymorphism associated with the genetic disposition (page 4, paragraph [0032]). The microassay kit with nucleic acid sequences immobilized on a solid support would involve screening by hybridization detection (fluorescent or radioactive signal upon duplex formation). Alternatively, the kit would include primer pairs that anneal to the nucleic acid sequences encoding proteins involved in insulin secretion. The primer pairs specifically anneal to flanking regions of the genes that putatively contain mutations associated with type 2 diabetes (page 4, paragraph [0032]).

Lee et al. do not discuss a kit comprising a probe comprising its 5' end labeled with a fluorescent dye, and in which fluorescence of the fluorescent dye decreases upon hybridization.

The teachings of Crockett et al. are discussed above, including the instant claims 7-9, using a single 5'-fluorescein probe specific for a single nucleotide polymorphism which decreases in fluorescence upon hybridization.

One of ordinary skill in the art would have been motivated to modify the method of Lee et al. to use a fluorescein which decreases in fluorescence upon hybridization to label the probe and use the labeled probe in a melting curve analysis to detect the mutation because not only do Crockett et al. demonstrate the ability to design singly labeled 5' fluorescein probes that optimize quenching during hybridization to

specific targeted polymorphisms, they also state that "fluorecein quenching probes are very easy to design, synthesize, and use in real-time PCR applications. They are more specific than double-strand DNA dyes like SYBR Green 1 and, unlike other internal probes, do not require the synthesis of a quencher on the same molecule," and furthermore, "single-labeled fluorescein probes provide a simple means of probe-based quantification and allele typing" (page 96, last paragraph). The skilled artisan would have had a reasonable expectation of success in labeling the probe of Lee et al. with a fluorescein which decreases in fluorescence upon hybridization, use the labeled probe in a melting curve analysis to detect the mutation, and include it in their kit. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the claimed probe and label it with a fluorescein which decreases in fluorescence upon hybridization, and use it in a melting curve analysis for mutation detection therein.

SUMMARY

5. No Claims are free of the prior art.

CONCLUSIONS

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

MEB 12/6/06

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

12/7/06